Association of genetic variation in Wnt signaling pathway gene (β-catenin) with susceptibility of Leukoaraiosis

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Background

the role of wnt/ β-catenin pathway as a key regulator of the BBB and it seems, therefore, a good candidate gene for LA.

- **periventricular white matter (PVWM)**
0 = absent
1 = “caps” or pencil-thin lining
2 = smooth “halo”
3 = irregular periventricular signal extending into the DWM
- **deep white matter (DWM)**
0 = absent
1 = punctate foci
2 = beginning confluence
3 = large confluent areas

Method

- Study population
Total of 339 LA cases (LA-PVWM, 183; LA-DWM 156) vs controls (LA-PVWM, 203; LA-DWM 230)
- Genotyping
Three single-nucleotide polymorphisms (SNPs), rs1880481C>A (SNP1), rs13072632 C>T (SNP2) and rs4135385 A>G (SNP3), were genotyped by RT-PCR with LightCycler 2.0 RT-PCR (Roche, Germany).

Results

Table 1. Demographic and clinical characteristics in control and patients with LA

Characteristics	Control (n= 203)	LA-PVWM (n= 183)	p	Control (n= 230)	LA-DWM (n=156)	p
Age	61.66 ± 13.01	74.46 ± 7.76	< 0.001	63.86 ± 13.25	73.44 ± 8.87	<0.001
Gender (M), n (%)	127 (62.6%)	91 (49.7%)	0.11	143 (62.2%)	75 (48.1%)	0.006
Hypertension, n(%)	112 (55.4%)	134 (73.2%)	<0.001	133 (58.1%)	113 (72.4%)	0.004
Diabetes, n (%)	58 (28.7%)	65 (35.5%)	0.153	71 (31.0%)	52 (33.3%)	0.63
Cholesterol (mg%)	166.13 ± 43.51	169.21 ± 41.13	0.477	166.66 ± 43.15	168.97 ± 41.25	0.62
Triglyceride (mg%)	147.12 ± 130.59	134.62 ± 104.08	0.201	148.80 ± 130.52	126.46 ± 98.13	0.07
HDL-Chol (mg%)	40.40 ± 10.88	41.26 ± 12.02	0.459	40.43 ± 10.75	41.36 ± 12.37	0.43
LDL-Chol (mg%)	98.43 ± 34.89	97.92 ± 31.90	0.881	98.08 ± 34.65	98.36 ± 31.47	0.93
Chol/HDL	4.28 ± 1.21	4.31 ± 1.28	0.802	4.29 ± 1.23	4.30 ± 1.26	0.96
LDL/HDL	2.54 ± 0.95	2.51 ± 0.93	0.747	2.53 ± 0.95	2.51 ± 0.93	0.89
ApoA1 (mg%)	1.23 ± 0.78	1.19 ± 0.26	0.56	1.21 ± 0.72	1.20 ± 0.27	0.81
ApoB (mg%)	0.97 ± 0.29	0.93 ± 0.25	0.301	0.96 ± 0.28	0.92 ± 0.26	0.23
ApoA1/ApoB	0.84 ± 0.31	0.81 ± 0.27	0.367	0.85 ± 0.30	0.79 ± 0.27	0.06
Lp(a) (mg%)	30.42 ± 26.09	28.23 ± 26.13	0.46	31.12 ± 28.39	26.65 ± 21.86	0.14
Glucose (mg%)	144.80 ± 65.91	141.78 ± 81.78	0.693	145.28 ± 65.27	140.51 ± 85.08	0.54
HbA1C (%)	6.36 ± 3.53	6.21 ± 1.38	0.595	6.35 ± 3.34	6.19 ± 1.40	0.58
tHCy (μmol/L)	13.26 ± 6.30	14.34 ± 5.78	0.081	13.29 ± 6.30	14.48 ± 5.67	0.06

◆ These findings suggest that advanced age and hypertension are the aggravating factor for the LA and can influence the risk estimation of genetic factors in LA.

Table 4. Haplotype frequency of β-catenin in control an LA

Genotype	Control	LA-PVWM	OR (95%CI)	p-value
SNP1/SNP2/SNP3				
C-C-A	0.0059	0.0048	1.11 (0.05-7.92)	0.91
A-C-A	0.1242	0.201	0.9 (0.63-1.27)	0.33
C-T-A	0.493	0.2914	0.42 (0.31-0.57)	<0.0001
A-T-A	0	0.0465	40.7 (2.43-679.89)	<0.0001
C-C-G	0.0065	0.0041	0.156 (0.019-1.276)	0.05
A-C-G	0.0826	0.0251	0.285 (0.134-0.60)	0.0005
C-T-G	0.2828	0.4019	0.108 (0.06-0.188)	<0.0001
A-T-G	0.005	0.0252	5.09 (1.09-23.73)	0.021

Genotype	Control	LA-DWM	OR(95%CI)	p-value
SNP1/SNP2/SNP3				
C-C-A	0.0058	0.0035	0.5 (0.05-4.73)	0.52
A-C-A	0.1296	0.2141	1.82 (1.24-2.67)	0.0019
C-T-A	0.4558	0.3004	0.51 (0.37-0.69)	<0.0001
A-T-A	0.0066	0.0494	7.69 (2.20-26.81)	0.0002
C-C-G	0.0073	0.0036	0.5 (0.05-4.73)	0.52
A-C-G	0.066	0.0321	0.47 (0.22-0.98)	0.04
C-T-G	0.3289	0.3657	1.17 (0.87-1.59)	0.28
A-T-G	0	0.314	31.97 (1.86-548.0)	0.0001

Conclusion

This study provides evidence of genetic polymorphisms of β-catenin are associated with susceptibility of LA, that will be one of the contributing factors in underlying mechanism of the LA .

Table 2a. Comparison of genetic frequency of β-catenin polymorphisms in the control and LA-PVWM

Genotypes	Control (n= 203,%)	LA-PVWM (n= 183,%)	OR (95%CI), p	AOR (95% CI), p
SNP1				
CC	125 (61.6)	93 (50.8)	1.0 (Reference)	1.0 (Reference)
AC	70 (34.5)	71 (38.8)	1.36 (0.89-2.086),0.15	1.14 (0.69-1.89),0.58
AA	8 (3.9)	19 (10.4)	3.19 (1.33-7.61),0.006	2.37 (0.82-6.84),0.108
Dominant				
CC vs AC+AA	125/78	93/80	1.55 (1.03-2.32),0.033	1.28 (0.79-2.07),0.30
Recessive				
CC+AC vs AA	175/8	167/19	2.48 (1.061-5.84),0.0312	2.35 (0.84-6.53),0.105

SNP3				
AA	83 (40.9)	51 (27.9)	1.0 (Reference)	1.0 (Reference)
AG	87 (42.9)	97 (53.0)	1.81 (1.15-2.85),0.0097	1.87 (1.81-3.23),0.022
GG	33 (16.3)	35 (19.1)	1.76 (0.95-3.113),0.068	1.62 (0.80-3.27),0.17
Dominant				
AA vs AG+GG	83/120	51/132	1.79 (1.16-2.74),0.0073	1.79 (1.07-2.98),0.0247
Recessive				
AA+AG vs GG	170/33	148/35	1.21 (0.72-2.05),0.45	1.12 (0.60-2.10),0.70

Table 2b. Comparison of genetic frequency of β-catenin polymorphisms in the control and LA-DWM

Genotypes	Control (n=230, %)	LA-DWM (n=156, %)	OR (95%CI), p	AOR (95% CI), p
SNP1				
CC	146 (63.5)	72 (46.2)	1.0(Reference)	1.0 (Reference)
AC	75 (32.6)	66 (42.3)	1.78 (1.15-2.75),0.008	1.64 (1.02-2.63),0.039
AA	9 (3.9)	18 (11.5)	4.05 (1.73-9.47),0.0006	3.31 (1.32-8.32),0.01
Dominant				
CC vs AC+AA	146/84	72/84	2.02 (1.34-3.067),0.0008	1.83 (1.17-2.88),0.008
Recessive				
CC+AC vs AA	221/9	138/18	3.20 (1.39-7.32),0.0039	2.72 (1.10-6.71),0.029

SNP3				
AA	92 (40.0)	42 (26.9)	1.0 (Reference)	1.0 (Reference)
AG	91 (39.6)	93 (59.6)	2.23 (1.40-3.56),0.0006	2.34 (1.38-3.95),0.0014
GG	47 (20.4)	21 (13.5)	0.97 (0.52-1.83),0.94	0.82 (0.41-1.65),0.59
Dominant				
AA vs AG+GG	92/138	42/114	1.81 (1.16-2.81),0.008	1.79 (1.10-2.91),0.018
Recessive				
AA+AG vs GG	183/47	135/21	0.60 (0.34-1.06),0.077	0.50 (0.27-0.93),0.02

- ◆ The genotype distribution of SNP1 and SNP3 were significant different among both LA and control.
- ◆ AOR: from logistic regression analysis with respect to age, sex, and hypertension.

Table 3. Combinatorial effects in LA and control according to the β-catenin genetic polymorphism

Genotype	Control	LA-PVWM	OR (95%CI)	p
SNP1/SNP3				
CC/AA	53	16		
AC/AG	35	43	4.0 (1.99-8.3)	<0.0001
AC/GG	9	6	2.2 (0.68-7.15)	0.17
AA/AG	1	4	13.25 (1.38-127.2)	0.0057
AA/GG	3	2	2.20 (0.33-14.4)	0.39
(AC+AA)/(AG+GG)	48	55	3.79 (1.92-7.49)	<0.0001

Genotype	Control	LA-DWM	OR (95%CI)	p
SNP1/SNP3				
CC/AA	57	12		
AC/AG	36	42	5.54 (2.57-11.91)	<0.0001
AC/GG	9	6	3.16 (0.99-10.58)	0.053
AA/AG	1	4	19.0 (1.94-185.5)	0.001
AA/GG	3	2	3.16 (0.47-21.06)	0.21
(AC+AA)/(AG+GG)	49	54	5.23 (2.51-10.90)	<0.0001